

Please substitute the paragraph beginning on page 2 at line 18 with the following rewritten paragraph:

B2 Due to the development in the field of purification techniques it has been possible to isolate and partially also characterize additional components from the bromelaine mixture. Thus, it was disclosed by Harrach et al. in The Journal of Protein Chemistry 14 (1995), 41-52, that bromelaine contains at least 8 basic proteases, which could be fractioned by means of FPLC-cation exchange-chromatography. Also, the existence of two forms of acidic proteases could be shown (Maurer et al., Journal of Protein Chemistry 17 (1998), 351-361).

Please replace the paragraphs beginning on page 3 at line 17 with the following rewritten paragraphs:

B3 It has been shown that especially the production of plasmin is stimulated by the bromelaine proteases, while the formation of fibrin and the adhesion of thrombocytes on endothelium cells – all of which are processes playing a significant role in blood coagulation – are inhibited.

In a preferred embodiment of the invention especially basic proteases are applied for the indicated purpose, preferably the bromelaine proteases obtained as fractions F4, F5 or, more preferably, F9 in accordance with the method described by Harrach et al. in the Journal of Protein Chemistry 14 (1995), 41-52.

Please replace the paragraph beginning on page 4 at line 28 with the following rewritten paragraph:

B4 The proteases can be isolated in accordance with conventional methods. Especially a purification as indicated by Harrach et al. in the Journal of Protein Chemistry 14 (1995), 41-52 and by Maurer et al. in the Journal of Protein Chemistry 17 (1998), can be applied. Upon purification, said proteases can be initially sequenced, and the corresponding gene can be isolated from the genome of e.g. the pineapple by means of molecular-biological methods. By means of molecular-biological methods a recombinant protein can then be provided in a conventional manner.

Please replace the paragraph beginning on page 5 at line 8 with the following rewritten paragraph:

The proteases used in the present invention, especially the basic proteases, are isolated according to Harrach et al., The Journal of Protein Chemistry 14 (1995), 41-52 and according to Maurer et al., The Journal of Protein Chemistry 17 (1998). The contents of said publications are herewith entirely included in the contents of disclosure of the present application.

B5 As disclosed in Harrach (1995), crude bromelain extracts from pineapple stems (*Ananas comosus*) were fractionated by two-step FPLC-cation-exchange chromatography. At least eight basic proteolytically active components were detected. The two main components F4 and F5 together with the most active proteinase fraction F9 were characterized by SDS-PAGE, mass spectroscopy, multizonal cathodal electrophoresis, partial amino acid sequence, and monosaccharide composition analysis. F9 amounts included about 2% of the total protein and had a 15 times higher specific activity against the substrate L-pyroglutamyl-L-phenylalanyl-L-leucine-p-nitroanilide (PFLNA) than the main component F4. The molecular masses of F4, F5, and F9 included 24,397, 24,472, and 23,427, respectively, as determined by mass spectroscopy. Partial N-terminal amino acid sequence analysis (20 amino acids) revealed that F9 differs from the determined sequence of F4 and F5 by an exchange at position 10 (tyrosine serine) and position 20 (asparagine glycine). F4 and F5 contained fucose, N-acetylglucosamine, xylose, and mannose in ratio of 1.0:2.0:1.0:2.0, wherein 50% of the proteins appeared to be glycosylated, F9 was found to be unglycosylated. Polyclonal antibodies (IgG) against F9 detected F4 and F5 with tenfold reduced reactivity. The pH optimum of F4 and F5 was between pH 4.0 and 4.5. For F9, the pH optimum was close to neutral pH. The kinetic parameters for PFLNA hydrolysis were similar for F4 ( $K_m$  2.30 mM,  $k_{cat}$  0.87 sec<sup>-1</sup>) and F5 ( $K_m$  2.42 mM,  $k_{cat}$  0.68 sec<sup>-1</sup>), and differed from F9 ( $K_m$  0.40 mM,  $k_{cat}$  3.94 sec<sup>-1</sup>).

As disclosed in Maurer (1998), two forms of an acidic bromelain proteinase isolated from crude bromelain, an extract from pineapple stem, were found by a two-step FPLC purification procedure. The basic main components were removed by cation exchange chromatography and the breakthrough fraction was further resolved by anion exchange chromatography into 15 protein fractions, only two of which, called SBA/a and SBA/b, were proteolytically active. These components were characterized by electrospray mass spectroscopy (ESMS), isoelectric focusing, N-terminal amino acid sequence analysis, monosaccharide analysis, and enzymatic